Sympathetic Nervous Activation in Essential Hypertension
Commonly Neglected as a Therapeutic Target, Usually Ignored as a Drug Side Effect

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Inappropriate and excessive activation of the sympathetic nervous system has been invoked as a cause of coronary heart disease. This pathophysiological linkage can take 2 forms. The most direct and explicit is when acute sympathetic nervous activation triggers adverse cardiac events (myocardial infarction, atrial fibrillation, ventricular arrhythmias, and Takotsubo cardiomyopathy have all been documented) during acute severe mental stress. Systematic evidence has been gathered at times of disasters, including war, missile attacks on civilians, and earthquakes, that strongly supports this proposition. The recently published and already celebrated analysis of coronary heart disease clinical presentations in German nationals in Munich during the 2006 Fédération Internationale de Football Association World Cup provides a telling example in demonstrating a dose-response relationship of the level of acute mental stress (judged from the closeness of the contest and the particular relevance of the result to Germany), and presumably sympathetic nervous activation, to cardiac events.2

The case is no less strong that chronic sympathetic activation is similarly adverse. In patients with heart failure, the cardiac sympathetic outflow is preferentially and often very highly activated. The level of this stimulation of the cardiac sympathetic outflow is directly related to reduced survival.3 β-Adrenergic blocking drugs break this link. Similarly, in patients with end-stage renal disease, the very high level of sympathetic activity, which is equal to that present in heart failure, almost certainly contributes directly to cardiovascular mortality.4 A similar claim has been made for depressive illness that the sympathetic activation present in the heart5 of the renal sympathetic nerves in patients with drug-resistant hypertension suggests that this activation of the sympathetic nervous system sustains the blood pressure elevation.6 Perhaps this sympathetic nervous activation in essential hypertension, much as for cardiac failure, contributes directly to mortality, having a detrimental influence in addition to the blood pressure elevation.7 If this is true, the sympathetic nervous system activation produced by some antihypertensive drugs (diuretics and dihydropyridine calcium channel blockers being examples8,9) might be harmful.

These considerations provide the backdrop to the interesting article by Wray and Supiano,10 who studied the effect of chronic oral dosing with hydrochlorothiazide on sympathetic nervous system activity in patient with hypertension and compared this with the effect of aldosterone antagonism with spironolactone. The patients with hypertension studied were elderly, the authors reasoning that, in the elderly, any drug-induced sympathetic activation would be doubly pertinent, superimposed as it would be on the sympathetic activation, which accompanies aging. Very emphatically, the sympathetic nervous activation anticipated with spironolactone was not seen, with clear cut sympathetic inhibition being documented. This was surprising given the contrary effect on sympathetic tone seen with sodium depletion produced by either a diuretic8 or dietary sodium restriction.11 Brain mineralocorticoid receptors mediating excitation of central nervous system sympathetic outflow have been described12; the effect of antagonizing these (lowered sympathetic tone) must have overridden any sympathetic stimulation from sodium depletion. Perhaps this sympathetic inhibition contributed to the blood pressure reduction being greater with spironolactone than hydrochlorothiazide in the study by Wray and Supiano.10 The sympathetic activation from sodium depletion, which preferentially involves the renal sympathetic outflow,11 is adaptive, promoting a counterbalancing renal retention of sodium.6

Of the differing methods used for investigating the sympathetic nervous system in clinical research, each have strengths and weaknesses.8 The method used by Wray and Supiano,10 a 2-compartment radiotracer kinetic method, has definite strengths, but perhaps one weakness. The principal strength is that the appearance rate of the sympathetic transmitter, norepinephrine, in the extravascular space, “NE2” in the authors’ notation, can be measured. This provides very specific information on whole body norepinephrine flux into the sympathetic synapse and beyond into the interstitial space. The measured value is larger, and the measurement has somewhat greater analytic power than the commonly used whole body norepinephrine “spillover” measurement,8,11 which represents the appearance rate of norepinephrine in the plasma (vascular) compartment. Wray and Supiano10 found that spironolactone lowered the appearance rate of norepinephrine in the extravascular space but did not materially
reduce norepinephrine spillover to plasma. The former is the more instructive measurement, and the finding is to be trusted.

But there is one limitation with their technique that, in contrast to measurement of regional norepinephrine spillover from individual organs and clinical microneurography measuring the sympathetic neural discharge in efferent fibers passing to the skeletal muscle vasculature, provides no information on regional sympathetic outflows. Sympathetic nervous system responses are sometimes regionalized, where one sympathetic outflow may be activated although another may be unchanged or inhibited. Sodium depletion in humans, in fact, provides a case in point, activating the renal sympathetic outflow but leaving the cardiac sympathetic outflow unchanged. What effect spironolactone has on sympathetic outflow but leaving the cardiac sympathetic outflow unchanged is a matter of discussion. Does the drug inhibit the renal sympathetic outflow, which might reduce cardiac risk in those elderly patients with essential hypertension who have prevailing high levels of cardiac sympathetic activity? The answer to both questions may well be “yes,” but the methodology does not allow us to be sure.

Let us return to the premise that persisting high sympathetic nervous system activity constitutes a cardiac “risk factor.” This is plausible but perhaps needs to be established on a case-by-case basis. One determinant might be the regional pattern of sympathetic activation, specifically whether the cardiac sympathetic outflow is activated. This applies with the sympathetic activation accompanying cardiac failure and depressive illness but not with that caused by sodium depletion or obesity. Another prerequisite might be whether myocardial injury exists, as it does in heart failure, to provide a fertile field for sympathetically mediated cardiac complications. Another factor of importance no doubt is the level of cardiac sympathetic nerve firing, which is very high indeed in cardiac failure. In essential hypertension, the level of activation of the cardiac sympathetic outflow is sufficient to contribute to the development of left ventricular hypertrophy and perhaps also to atrial fibrillation. Consideration of the efficacy and safety of dihydropyridine calcium channel blocking antihypertensive drugs, however, indicates that chronic sympathetic nervous system stimulation is not invariably harmful. Suspicions that the chronic sympathetic activation produced by this drug class may be toxic to the heart, even with the currently used longer acting drug formulations, were soundly disproved in the recent Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension Trial.

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References
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